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09/487,790	01/20/2000	Raphael Gorodetsky	995/46	3576

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,790	GORODETSKY ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7 and 10-21* is/are pending in the application.

4a) Of the above claim(s) *7 and 13-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1, 7, and 10-21 are pending.

The amendment filed 6/9/05, which amends claims 1, 7, 10, 17 and 20, cancels claims 2-6 and 8-9, has been entered.

This application contains claims 7 and 3-21 drawn to an invention nonelected with traverse in the office action mailed 3/11/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Thus, pending claims 1 and 10-12 are examined in this Office action.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Objection to claims/the specification

The disclosure is objected to because of the following informalities:

In claim 1, "wherein the polypeptide or analogue" should be changed to "wherein the polypeptide or functional analogue". See also claim 10.

The specification is objected to because the continuing data of the current application is missing.

The drawings are objected to because the following reasons. The drawings of Figure 2 A-B, and Figure 3 A-D look obscure. Also, Figure 7 A-E does not appear to clearly present the data of proliferative response to HF (see the data showing error bars appear to be hidden in "grey areas"). The corrected drawings are required.

In the brief description for Figure 5 (page 16), "FIG. 5A, 5B and 5B" should be changed to "FIG. 5A, 5B and 5C". In addition, the said description for Figure 5 C appears to be absent.

In the brief description for Figure 7 (pages 16-17), indication of panels "A", "B", "C", "D" and "E" should be made after "Cβ (SEQ ID NO:1)", "CαE (SEQ ID NO:3)", "preCα (SEQ ID NO:2)", "Cα (SEQ ID NO:4)" and "Cγ (SEQ ID NO:5)", respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 10-12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a new matter rejection for the following reasons:

The amended claims 1 and 10 recitation "at least one amino acid *substituted by a natural or synthetic amino acid*" represents a departure from the specification and the claims as originally filed since the specification (page 10, lines 14-16) only set forth "at least one amino acid substituted into a naturally occurring or non-naturally occurring amino acid" but not by "synthetic amino acid" thereof.

The recitation of instant claims was not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in

the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 1 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the polypeptide comprising SEQ ID NO:1 having haptotatic activity, does not reasonably provide enablement for a functional analog to the SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2) The nature of the invention:

The current invention is directed to a polypeptide which is a functional analogue comprising the mutated SEQ ID NO:1 wherein the mutation is substitution and a composition comprising the said functional analogue. The analogue encompasses a large number of variants:

(i) any polypeptide comprising SEQ ID NO:1 having amino acid substitution(s) in combination with variable that the fibrinogen β-chain molecules vary from species to species;

(ii) any molecule analogous (functionally and/or structurally) to SEQ ID NO:1 having haptotactic activity; the said molecule encompasses the compound comprising a polypeptide differing in a range from one to all amino acid residues of a full-length β-chain fibrinogen protein of any species; and

(iii) any cross-linked polypeptide molecule comprising fibrinogen α and/or γ chain(s) as well as the β-chain subsequence of SEQ ID NO:1 through disulfide linkage(s). For covalent linkages between α, γ and β-chain of fibrinogen, see Henschen et al. (*Ann. N. Y. Acad. Sci.* (1983) 408, 28-43).

Screening and characterization of the above-stated variant molecules needs undue experimentation.

In addition, the current claim language "*other than an entire fibrinogen β-chain*" reads on a large quantity of subsequence/fragments of the full-length β-chain amino acid sequence (462 amino acids) in range from 21 to 461 amino acid residues. The screening of "pool" of the said subsequence/fragments also requires undue experimentation.

(3) The unpredictability of the art:

The variant molecules would be expected to have unpredictable properties. This is because, substitution mutation has, in general, negative impact on the mutated molecule as evidenced by that missense mutations in human β-chain fibrinogen cause abnormal biological activity compared with the wild-type β-chain thereof (see Duga et al. (2000) *Hemostasis Thrombos. Vascul. Biol.* 95, 1336-1341).

The specification does not provide direction as to (i) size of the analogue; (ii) covalent structure including core domain critical for the said haptotatic activity; and (iii) multimer (e.g.,

αβγ trimer of a variant fibrinogen) of the analogue polypeptide; and thus, screening the activity thereof is not predicatable. It is of note that the current language "*the polypeptide other than an entire fibrinogen β-chain*" reads on any biopolymer molecule that is not an *entire fibrinogen β-chain* but comprises polypeptides including covalently linked (variant) αβγ chains of fibrinogen and/or other biopolymer. Substitution with by cysteine residue, for instance, would result in formation of inter- and/or intra-molecular disulfide bonds between the analogue polypeptides or between the analogue and γ-/α-chains of fibrinogen. The specification does not teach whether or not such the analogue polypeptide have the haptotatic activity.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to teach common attribute and characteristics that identify the variant or subsequence of the functional analogue. The specification needs to provide sufficient guidance to be considered enabling.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the variety of variant or the functional analogue.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in mutagenesis, protein engineering as well as knowledge in hematology and skill in peptide synthesis. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to make and characterize the functional analogues comprising substitution mutations (variants) in and/or not in the SEQ ID NO:1 and the pharmaceutical composition comprising said variants.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "*functional analogue*"; the recitation is not apparent since the specification insufficiently define it, and because it ambiguously refers to (i) an analogue having no sequence identity to the instant SEQ ID NO:1 but haptotatic function; (ii) an analogue having immunological function of binding to antibody which recognizes a β-chain sequence, e.g., SEQ

ID NO:1; (iii) an analogue having activity of promoting healing of wound, or, (iv) an analogue having activity of involving in cell proliferation or a chemotactic action (see page 9 of the specification). See also claim 10.

Claim recites "... *other than an entire fibrinogen β-chain* ". The recitation is unclear because the entire fibrinogen β-chain sequence vary upon different species (see Table 2, panel A, page 21 of the specification); without reciting a fibrinogen β-chain from *a* particular species, "other than ..." is considered indefinite. Indication of from which species the fibrinogen is obtained therefore is required in order to determine sequence structure of "the polypeptide" which is other than the *entire fibrinogen β-chain* from that species.

Claim 10 "a composition" is not apparent as to whether or not it refers to the protein/polypeptide composition, or the pharmaceutical composition of claim 11, or solid support composition (e.g., chromatographic column) comprising the polypeptide. The dependent claims 11 and 12 are also rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 10-12 are rejected under 35 U.S.C. 102 (a) as being anticipated by Gorodetsky et al. (WO99/61041).

In the patent claim 1, Gorodetsky et al. discloses a β-fibrinogen C-terminal peptide comprising "KGSWYSMRKMSMKKIRPFFPQQ" identical to the instant SEQ ID NO:1; the said peptide has haptotactic activity, e.g., having cell adhesive effect (see page 6, lines 27-30), which anticipates instant claim 1.

In the patent claim 4, Gorodetsky et al. teach a composition comprising said peptide, which anticipates instant claim 10.

In the patent claim 5, Gorodetsky et al. discloses that said composition comprising a pharmaceutically acceptable carrier, which anticipates instant claim 11.

In the patent claim 6, Gorodetsky et al. discloses that said composition comprising a biological agent, which anticipates instant claim 12.

Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Henschen et al. ("human fibrinogen sequence, sulfur bridge, glycosylation and some structural variants", in "*Protides of the biological Fluids*" (1980) *Proc. 28th Colloq.*, Peeters, H., ed., pp.51-56).

Henschen et al. teach a variant (human) β-chain fibrinogen which differs from the entire human β-chain thereof in its N-terminal region (see Figure 8), and which comprises intact C-terminal section that comprises the subsequence identical to the instant SEQ ID NO:1 ("KGSWYSMRKMSMKKIRPFFPQQ") possessing haptotactic activity. The Henschen et al. teaching anticipates instant claim 1.

It is of note that claim1 as written encompasses any analogue polypeptide comprising SEQ ID NO:1 (see the above statement of the rejection under 35 USC 112, first paragraph)

including any variant polypeptides differing (including single amino acid alteration) from the any full-length β-chain fibrinogen from any species. In light of this, the above rejection is applicable.

Claim 1, 10 and 12 are rejected under 35 U.S.C. 102 (b) as being anticipated by Yee et al. (structure (1997) 5, 125-138) as evidenced by the known fact that the peptide consisting of "LTIGEGQQHHLGGAKQAGDV" has haptotatic activity (see page 13, lines 8-9, Gorodetsky et al. (WO 99/61041)).

Yee et al. teach a haptotatic polypeptide, a recombinant 30kDa C-terminal fragment of the human fibrinogen γ chain (rFbgγC30) consisting of residues Val143-Val411 (see page 126, the left column, the last paragraph). This rFbgγC30 polypeptide comprising "RLTIGEGQQHHLGGAKQAGDV" (residues Leu391 - Val411, see Figure 4) which has identical length to the instant SEQ ID NO:1 and is a substitution mutant of the instant SEQ ID NO:1 (KGSWYSMRKMSMKKIRPFFPQQ) wherein all residues have been substituted (note that the current claim language "*that has at least one amino acid substituted by ...*" reads on all amino acids are substituted). The rFbgγC30 polypeptide has haptotatic activity because said polypeptide comprising haptotatic sequence "LTIGEGQQHHLGGAKQAGDV" (residues Leu392-Val411) as is evidenced by the Gorodetsky et al. The above Yee teachings anticipate instant claim 1.

Yee et al. teach a crystal composition comprising the rFbgγC30 polypeptide (see "*Materials and methods*" section, page 135), which anticipates instant claim 10.

In "*Materials and methods*" section, Yee et al. teach a chemical composition comprising the rFbgγC30 polypeptide and a biological agent, recombinant human factor XIIIa, which anticipates instant claim 12.

Claim 1 and 10 are rejected under 35 U.S.C. 102 (b) as being anticipated by Mayo et al. (*Biochemistry* (1990) 29, 3277-3286) as evidenced by the known fact that the peptide consisting of "LTIGEGQQHHLGGAKQAGDV" has haptotatic activity (see page 12 of Gorodetsky et al. (WO 99/61041)).

Mayo et al. teach a haptotatic peptide, a human fibrinogen γ chain, residues 385-411 (KIIPFNRLTIGEGQQHHLGGAKQAGDV) (see abstract) wherein subsequence "RLTIGEGQQHHLGGAKQAGDV" has identical length to the instant SEQ ID NO:1 and is a substitution mutant form of the instant SEQ ID NO:1 (KGSWYSMRKMSMKKIRPFFPQQ) wherein all residues have been substituted (note that the current claim language "*that has at least one amino acid substituted by* ..." reads on all amino acids are substituted). The said peptide has haptotatic activity because said polypeptide comprising haptotatic sequence "LTIGEGQQHHLGGAKQAGDV" (residues Leu392-Val411) as is evidenced by the Gorodetsky et al. The above Mayo et al. teachings meets the claim 1 limitation and thus anticipate instant claim 1.

Yee et al. teach a chromatographic composition comprising the above-mentioned polypeptide and gel filtration column (see "*Materials and Methods*" section, page 3278), which anticipates instant claim 10.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claims 1 and 10-12 are rejected under 35 U.S.C. 102 (e) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) 35 U.S.C. 103(a) over Pandya et al. (J. *Biol. Chem.* (1985) 260, 2994-3000). As is evidenced by the fact that fibrinogen β-chain has C-terminal subsequence which is identical to the instant SEQ ID NO:1) as disclosed in Watt et al. (Biochemistry (1979) 18, 68-76).

Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable.

Pandya et al. teach a fibrinogen polypeptide comprising β-chain which lacks the first 42 amino acid residues of the full-length β-chain (meets the limitation of claim 1 "*wherein the polypeptide is other than an entire fibrinogen β-chain*"). Because the C-terminal residues 441-462 of the said polypeptide consists of the instant SEQ ID NO:1 (KGSWYSMRKMSMKKIRPF FPQQ) that has haptotatic activity and any polypeptide comprising the SEQ ID NO:1 should have the haptotatic activity, the Pandya et al. teachings anticipate the instant claim 1.

In "*Experimental procedure*" section, Pandya et al. teach a composition comprising the said polypeptide and 0.05 M Tris-buffer, pH 7.4 (see "Experimental procedure" section) in which the polypeptide is dissolved, which anticipates instant claim 10.

The said Tris-buffer is considered to be a pharmaceutically acceptable carrier, as applied to instant claim 11.

Pandya et al. teach a immunological composition comprising said polypeptide and a nonspecific antibody (see page 2995, the right column) which is a biological agent, as applied to instant claim 12.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber, Jon, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu, Ph.D.

Art Unit 1653, Examiner

July 27, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER